

MatVPC: A User-friendly Matlab Tool for the Automatic Construction of Visual Predictive Checks and Quantified Visual Predictive Checks of Systems Pharmacology Models



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Introduction

- Traditionally, quantitative pharmacology models are implemented and evaluated using PsN[®] (coupled with NONMEM[®]) or MONOLIX[®]
- Quantitative Systems Pharmacology (QSP) models are progressively entering the arena of contemporary pharmacology^{1,2}
- QSP models are usually complex and are, therefore, implemented in surrogate software, such as MATLAB[®]
- The efficient implementation of QSP models necessitates the development of flexible computational tools that are built into QSP mainstream software

Objectives

- To **develop** a versatile computational tool, MatVPC, that is built into QSP mainstream software and carries out simulation and evaluation of QSP models
- To **illustrate** the functionality of MatVPC through a pharmacokinetic (PK) model and a pharmacodynamic (PD) model
- To **validate** MatVPC against the gold standard tools in pharmacometrics community³, PsN[®] (with NONMEM[®]) and Monolix[®]

MatVPC Input

Step 1: Input model parameters and model equations

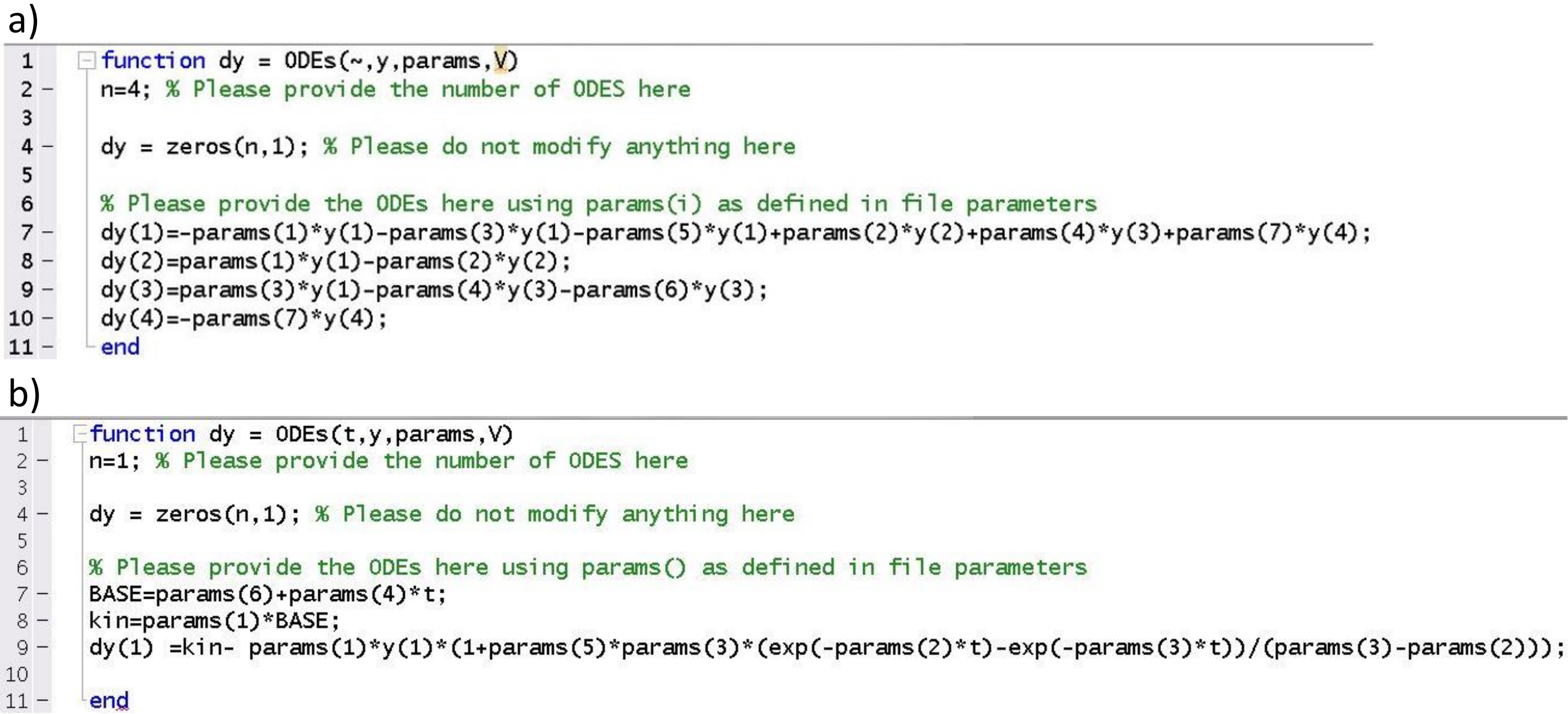


Figure 1: **Input of model equations in MatVPC.** **a)** Input of PK model equations and **b)** Input of PD model equations. In this file the user inputs the ODEs, along with potential algebraic equations, describing the quantitative pharmacology model. Please note that for the sake of space restriction, the files with the model parameters are not shown here.

Step 2: Input i) dataset name, ii) stratification variables and iii) model name

```
>> MatVPC('dataset name',{'stratification variable'})
```

Please provide the name of the model:model name

Would you like to plot from existing simulation file (y/n)?:n

Step 3: Choose methods and graphical settings

Figure 2: **Optional input in MatVPC for the PK model.** In this interface, the user can modify the default values of 40 characteristics of the VPC or QVPC plots. These characteristics are either method-related (e.g. ODE solver) or graphical settings (e.g. curve color). The VPC and QVPC plots shown in Figure 3 were constructed using the input values shown here.

Conclusions and Future Work

- MatVPC can be downloaded freely from <http://sourceforge.net/projects/matvpc/>
- MatVPC constitutes a useful addition to the openly available toolboxes exploited by quantitative as well as clinical pharmacologists
- MatVPC will be continuously advanced and its future versions will execute key analyses in systems pharmacology field, such as sensitivity analysis⁷ or model reduction⁸

References

- S.A. Visser et al., *CPT:PSP*, 2014
- M.C Peterson & M.M. Riggs, *CPT:PSP*, 2015
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- M. Lavielle & K. Bleakley, *Journal of Pharmacokinetics and Pharmacodynamics*, 2014
- T.M. Post et al., *Journal of Pharmacokinetics and Pharmacodynamics*, 2008
- S. Van Wart et al., ACoP meeting, San Diego, CA, 2011
- X.Y. Zhang et al., *CPT:PSP*, 2015
- A. Dokoumetzidis & L. Aarons, *IET Systems Biology*, 2009

Methods

- Unlike comparable tools, MatVPC is a unique all-in-one Matlab[®]-based tool that integrates the following:
 - It is publicly available
 - Constructs VPC plots of complex QSP models
 - Offers automatic binning of data using a rigorous approach⁴
 - Constructs QVPC⁵ plots of complex QSP models
 - Performs Monte Carlo simulations of the model and plots the results with any requested summary statistics
 - Accommodates any model independently of the software that has been built

Case studies:

- Three compartment PK model with observations from two studies:**
 - Study 1 (50 subjects): Single intravenous bolus dose
 - Study 2 (50 subjects): Single oral dose
 - Data were stratified by study and automatic binning was performed
- Highly non-linear PD model⁶ describing body weight with observations from two studies**
 - Study 1 (250 subjects): Sampling times: 0.78, 1.28, 1.35, 3.58, 4.48, 6.99, 7.42, 10.2
 - Study 2 (250 subjects): Sampling times: 0.78, 2.52, 2.59, 6, 6.1, 8.31, 9, 9.5
 - Data were stratified by study and automatic binning was performed

MatVPC Output (PK Model)

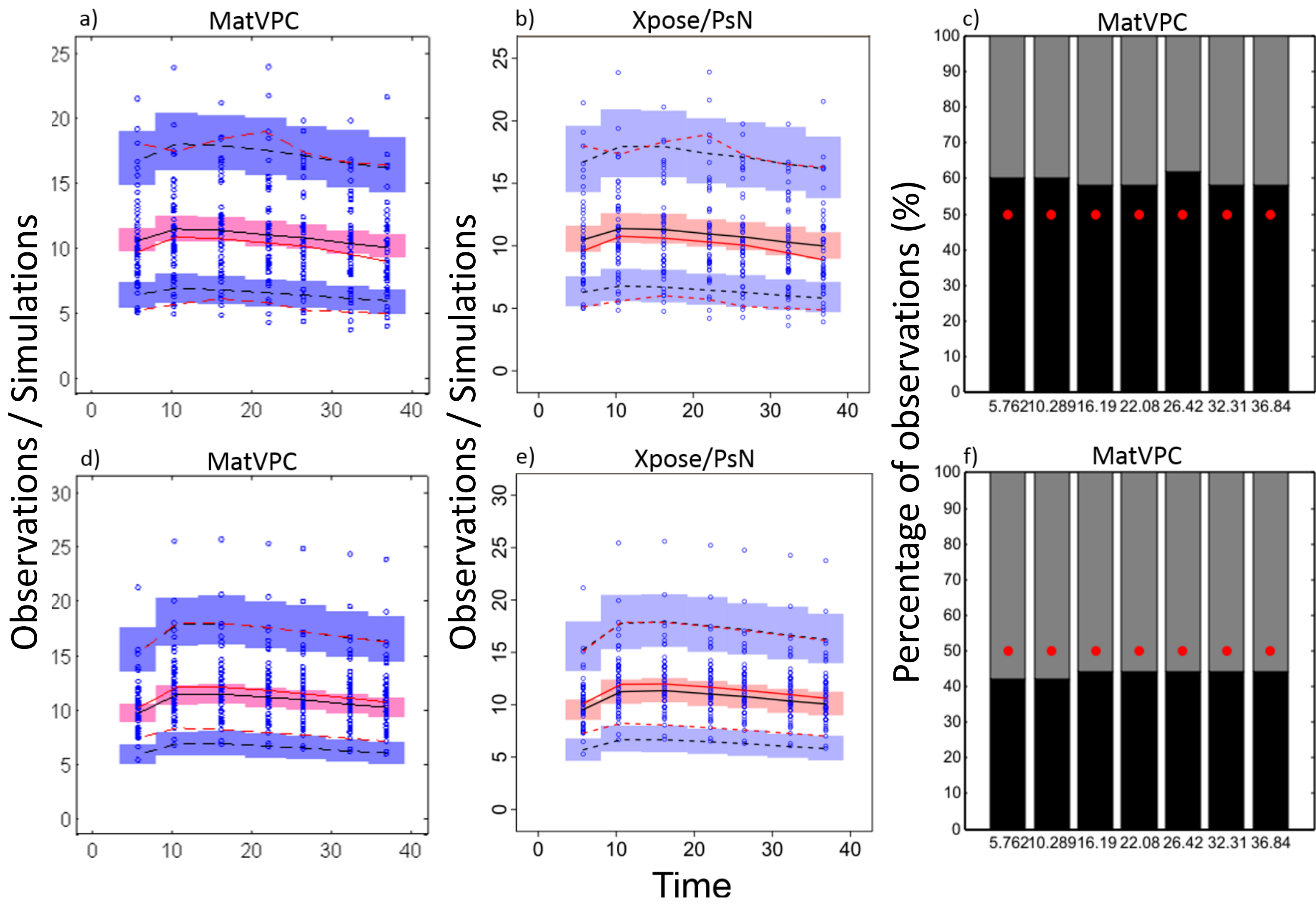


Figure 3: **VPC and QVPC plots.** **a,b,d,e)** VPC plots generated by MatVPC (a,d) and Xpose-PsN (b,e) showing the results from compartment two and study one (a,b) and two (d,e). Blue dots correspond to the observations. Red dashed lines correspond to the 90% percentiles of the observations whereas red solid lines correspond to the median of the observations. Black dashed lines correspond to the 90% percentiles of the simulations whereas black solid lines correspond to the median of the simulations. Blue shaded areas represent the 90% CI of the simulation 5th and 95th percentiles whereas pink shaded areas represent the 90% CI of the simulation median. **c,f)** QVPC plots of compartment two and study one (c) and two (f), as constructed by MatVPC. At each time point, the black bar presents the observed data below the model predicted median (red dots), whereas the dark grey bar shows the observed data above the model predicted median. The total of the black and grey bar combined presents the percentage of available data (here 100%).

MatVPC Output (PD Model)

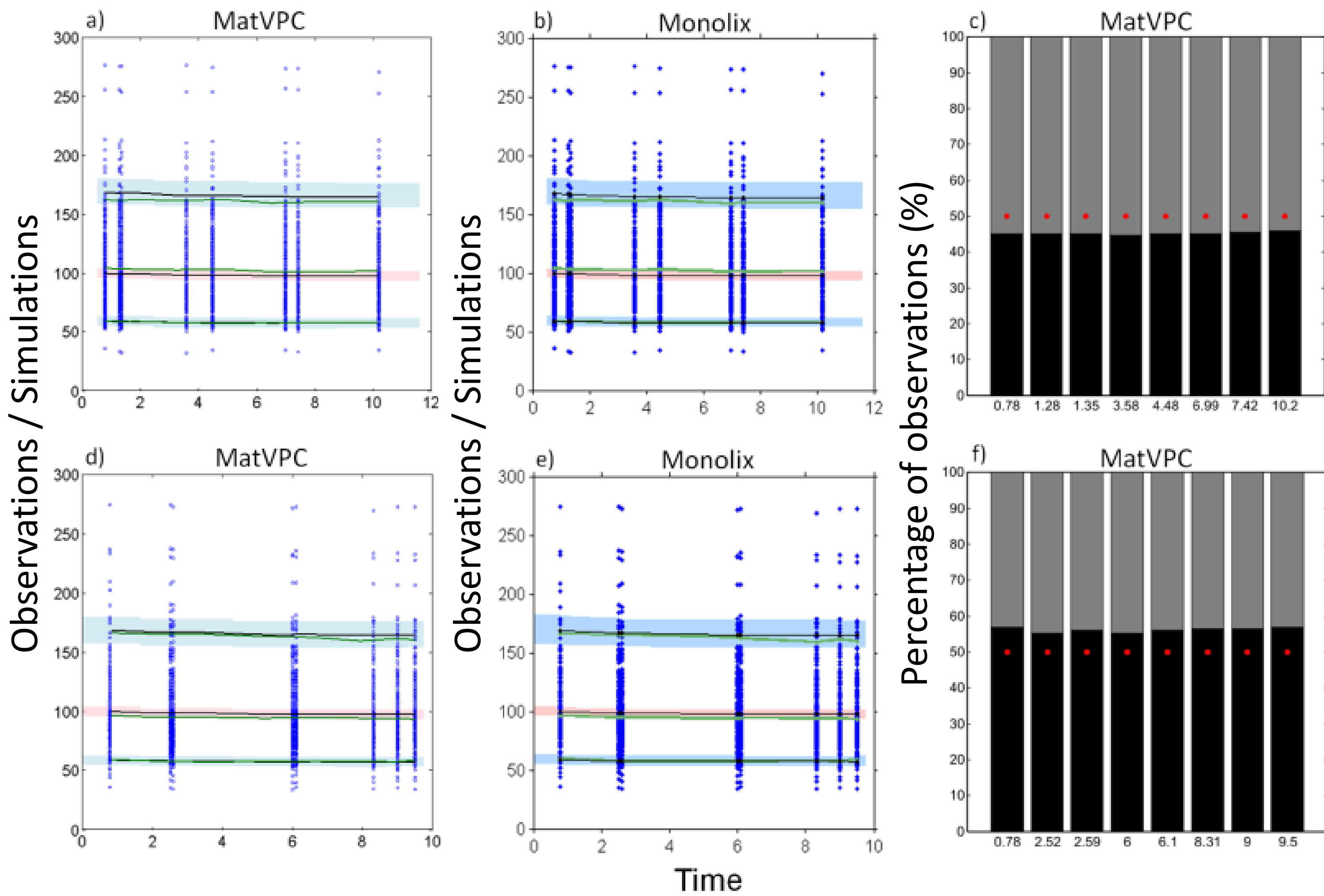


Figure 4: **VPC and QVPC plots.** **a,b,d,e)** VPC plots generated by MatVPC (a,d) and Monolix (b,e) showing the results from PD model and study one (a,b) and two (d,e). a,d) VPC plots of study one (a) and study two (d) generated by MatVPC. b,e) VPC plots of study one (b) and study two (e) generated by Monolix. Blue dots correspond to the observations. Green lines correspond to the 5th, 50th and 95th percentiles of the observations. Black lines correspond to the 5th and 95th percentiles of the simulations. Light blue shaded areas represent the 90% confidence intervals of the simulation 5th and 95th percentiles whereas pink shaded areas represent the 90% confidence intervals of the simulation median. **c,f)** QVPC plots of study one (c) and two (f), as generated by MatVPC. At each time point, the black bar presents the observed data below the model predicted median (red dots), whereas the dark grey bar shows the observed data above the model predicted median. The total of the black and grey bar combined presents the percentage of available data (here 100%).